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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,964	02/11/2002	Robyn Lynne Ward	01-1242	4441

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,964	WARD ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-167* is/are pending in the application.

4a) Of the above claim(s) *1-47 and 55-167* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/8/03, 3/10/03, 2*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

DETAILED ACTION

1. The Election filed September 27, 2005 in response to the Office Action of June 29, 2005 is acknowledged and has been entered. Applicants elected Group 3, SEQ ID NO:36 (claims 48-54) and fragment species about 5 and about 50 contiguous amino acids (claim 49) with traverse. All species for Group 3 have been rejoined for examination purposes (claims 49, 50, and 51).

Applicants traverse on the grounds that at least 10 sequences should be included in the search as is consonant with the Official Gazette, 1192 O.G. 68 (November 19, 1996) and MPEP 2434. This argument has been carefully considered but is not found persuasive because these guidelines were set forth nine years ago and the sequence data base and non patent literature to be searched have exponentially increased every year since 1996 making a search for 10 sequences an enormous search burden.

Claims 1-167 are pending. Claims 1-47 and 55-167 are withdrawn. Claims 48-54 are currently under prosecution.

Specification

2. The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the most current priority status of the present application, including proper reference to applications that have been issued or abandoned.

3. The disclosure is objected to because it does not comply with the sequence rules:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reasons(s) set forth on the attached Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. In particular, no sequence identifier is associated with the sequences disclosed on pages 42, 43, 48 - 50, 53, 66, and 67. Although Examiner has made an effort to identify where in the specification such informalities are found, it appears that the specification is replete with such informalities. Applicant must correct these informalities.

Applicant is given the period of reply for this Action within which to comply with the sequence rules, 37 CFR 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821 (g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the

provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 52 is rejected because it recites the phrase **"derived from"** to describe the origin of the peptide fragment from the complementarity determining region (CDR). This renders the claim indefinite because the phrase **"derived from"** is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear what the peptide fragment consists of. Given the above reasons, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 48-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a peptide fragment of the polypeptide of SQ ID NO:36 wherein said peptide induces an immune response when administered to a vertebrate (claims 48-51), wherein said peptide fragment is derived from the CDR (claim 52), wherein said immune response is an idiotypic response (claim 53), wherein the vertebrate is human (claim 54).

The specification discloses that the claimed peptide fragment is used as an idiotypic vaccine to treat tumors in vertebrates (p. 2, lines 7-10; p. 13, lines 4-17; p. 28, lines 34-35; p. 31, lines 11-17). The specification discloses that the claimed peptide fragment is the heavy chain fragment of an antibody that recognizes p53 (p. 6, lines 37-39; p. 69, Table V). The specification discloses that an antibody (Ab1) or fragment thereof may function as an immunogen and elicit a second antibody (Ab2) and T cell response against idiotypes of the original Ab1. The anti-idiotypic antibody Ab2 can induce anti-anti-idioptypic antibodies (Ab3) as well as T cells which may recognize the same epitopes as Ab1. Since Ab1 binds both the p53 epitope and Ab2, Ab2 mimics the structure of the antigenic epitope on p53. A proportion of Ab3 may augment and prolong the efficacy of the original antibody, Ab1. The specification discloses that induction of this anti-idiotypic network results in protection from metastases partly through the induction of p53-specific CTLs (p. 13, lines 5-17). The specification further discloses

that the claimed peptide fragments may or may not have affinity for a p53 protein or a portion thereof (p. 28, lines 26-27).

One cannot extrapolate the teaching of the specification to the enablement of the claims because it does not appear that the specification contemplates any use for the claimed peptide fragments other than as an anti-cancer vaccine. However, the specification discloses that the claimed peptide fragments may or may not have affinity for a p53 protein or a portion thereof and comprise a fragment of the heavy chain which may not comprise a CDR or all 3 CDR's necessary for binding the epitope of p53. The specification discloses that the "antigen recognizing portion" of an antibody is the variable region of an antibody or fragment thereof which is responsible for binding and/or recognizing the target antigen (epitope or idiotype) of the antibody and it includes the CDR regions to the whole variable region or a combination of these two regions (p. 19, lines 29-34). Although it is clear that binding specificity of the recombinant antibody is determined by the combined CDR regions in the variable domain of an antibody, it is equally clear that in the absence of the complete binding domain, one would not expect to produce an anti-idiotypic antibody response that would function as contemplated in the specification. Although drawn to humanization of antibodies, the teaching of Gussow et al (Methods in Enzymology, 1991, 203:99-121) are relevant to the instant rejection. In particular, Gussow et al teach that appropriate framework regions that house the CDRs are essential for providing the proper orientation for the CDRs to exhibit antigen specificity, for example Gussow et al teach that the applicability of antibody humanization techniques relies on, among others, the assumption that the frameworks

of the variable domains serve as a scaffold to support the CDRs in a specific way that facilitates antigen binding and further teach that it is of great importance to retain the interactions between the donor CDRs and the acceptor framework as closely as possible to the CDR-framework interactions of the original MAb and further disclose that the affinity of the first fully humanized antibody CAMPATH1 was nearly 40 fold lower compared to the original rat MAb, apparently because of differences of residues in the framework region of the humanized antibody compared to those of the original antibody, particularly those located close to the CDRs. Clearly, alteration of even one amino acid residue can alter the packing of the residues within the molecule as it was demonstrated that mutation of the human Ser 27 to a Phe (the residue found in the original rat antibody at this position) restored the binding affinity of the humanized antibody close to the original affinity (see page 100), thus alteration of even one amino acid residue altered the three dimensional structure of the antibody binding domain and therefore the binding domain of the antibody to the antigen. Given the reference teachings, it would be expected that a peptide fragment comprising about 5 contiguous amino acids of SEQ ID NO:36 would comprise less than a single CDR of an antibody and would clearly be less than the variable binding domain of the antibody, and a single CDR cannot comprise the binding domain of an antibody. It would be expected that a vaccine comprising about 5 contiguous amino acids of SEQ ID NO:36, or even 50 contiguous amino acids that are not required to even have affinity to p53 (a known tumor antigen) would NOT be effective as a vaccine against tumors because the peptide fragment

lacks the essential structures and regions required for an idiotypic response that would result in the induction of p53-specific antibodies or CTLs.

Further, it would be expected that a peptide fragment comprising about 5 contiguous amino acids of SEQ ID NO:36 (the heavy chain) would NOT comprise the binding region to an entire antigenic epitope of p53. In particular, MacDonald et al., (Proceedings of the European Society for Chlamydia Research, 1988, p. 140) teach that the active site of an antibody molecule (Ab1) has a distinct molecular configuration for each antigenic epitope and is termed an idiotype. Antibodies directed against this active site (anti-idiotype, Ab2) may be an internal image of the original antigen and can be used to stimulate immune responses (Ab3) to that antigen. Given the teachings of the reference, it is clear that in order to have an Ab2 binding site with the distinct molecular configuration for the antigenic epitope (that is the original epitope to which Ab1 bound) the antigen that produced that antibody would have to comprise the complete binding domain including both the heavy and light chain variable regions. Clearly, the claimed invention does not comprise the complete binding site of that antibody.

Further, it would not be possible to predictably determine which peptide fragments of SEQ IDNO:36 would actually induce antibodies or stimulate the anti-idiotypic network to produce antibodies that bind to p53 and generate an effective immune response against tumors. Roitt et al (1998, Immunology, 4th ed, Mosby, London) teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that

only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that "Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1)". Furthermore, this does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quaternary structure of a protein in a physiological situation. Further, there is no teaching in the specification of which part of SEQ ID NO:36 should be used to produce antibodies which will bind specifically to p53.

There is no teaching in the specification of whether or not the epitopes of SEQ ID NO:36 are linear or comprise 3-dimensional structures. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the specification fails to disclose sufficient guidance and objective

evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes recognized by the claimed invention. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937, 1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column). Chatterjee et al (1994, Cancer Immunol Immunother, 38:75-82) teach that it cannot be predicted that all Ab2 antibodies, even those that carry an internal image, will induce specific immunities and specifically teach that of seven anti-Ids which carried all of the typical immunochemical properties of an internal image, only one was able to induce antitumor immunity and further teach that similar experiences were met by other investigators and because of being negative results, often were not reported (p. 79, col 2). Since the specification has not identified which amino acids and or polypeptide fragments are critical or essential characteristics of the epitope, it would not be predictable, to one of relative skill in the art, that such methods employing agents would be specific for or able to bind to any epitopes on SEQ ID NO:36, hence the pathway of the idiotypic vaccine to produce induce the production of p53-specific CTLs by immunizing with peptide fragments of SEQ ID NO:36 would not likely result in anti-anti-idiotypic antibodies that recognize the antigenic epitope of p53.

Additionally, it would not be expected that a vaccine administered by immunizing with a peptide fragment of SEQ ID NO:36 would be effective against cancer because it would be expected, even if the peptide fragment were able to elicit an immune response against the anti-p53 antibody heavy chains as claimed, that the response would eliminate the apparent autoantibody p53 antibodies, reducing the population able to stimulate antibodies and T-cells and interfering with any possible anti-cancer activity of the auto antibodies.

Finally, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that a peptide fragment of SEQ ID NO:36 could be predictably used as an anti-cancer agent for cancer therapeutic strategies as inferred by the claims and as contemplated by the specification. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by

chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that a peptide fragment of SEQ ID NO:36 could be predictably used as an anti-cancer agent for cancer therapeutic strategies as inferred by the claim and as contemplated by the specification. In addition, anti-tumor agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The agent may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the agent. In addition, the agent may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the agent has no effect,

circulation into the target area may be insufficient to carry the agent and a large enough local concentration may not be established.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention would function as inferred and contemplated by the specification with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Continuation of Attachment(s) 6). Other: notice to comply to sequence rules.

Application No. 09/936964

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.